44. The method of claim 17, wherein the autoimmune response to a self antigen results in diabetes--

B3 concl'd.

REMARKS

Claims 1-24 and 27-32 were pending in the application. Claims 13-18, 20, 23, and 27 were under consideration. Claims 13-18, and 20 have been amended. Claims 1-12, 19, 21-24, and 27-32 have been cancelled without prejudice herein. Claims 33-44 have been added. Accordingly, after entry of this amendment claims 13-18, 20, and 33-44 will be pending in the application.

No new matter has been added. Support for the claim amendments can be found throughout the specification and in the claims as originally filed. Specifically, support for the language "immune response to a self antigen" and "which activates NK-T or CD25+ cells" can be found at least at page 3, lines 24-34. Support for the language "presented in the context of CD1 molecules" can be found at least at page 9, lines 16-17. Support for the language "further comprising administering an immunogen" and "further comprising administering a TH2 cytokine" can be found at least at page 19.

The Examiners remarks with respect to the Restriction Requirement dated June 10, 2002 are noted. Applicants note that, in contrast to the Examiner's comment on page 2 of the Office Action, the election was made with traverse. Applicants further acknowledge the Examiner's comment that the pending claims will be examined according to MPEP §§ 809 and 809.03 linking claim practice. Pursuant to MPEP §§ 809 and 809.03, Applicants understand that the

linking claim (claims 13 and 16) will be examined with the invention elected and should the claim be allowed, the restriction requirement will be withdrawn.

Objection to the Specification

The specification was objected to as failing to provide proper antecedent basis for "administrating an enhancing agent wherein the agent is a bacterial cell lysate." This objection is respectfully traversed. Administering an enhancing agent wherein the agent is a bacterial cell lysate is found at page 6, line 22 of the specification as filed. Accordingly, it is respectfully requested that this objection be reconsidered and withdrawn.

Objections to the Claims

Claim 16 was objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 16 has been amended to be in independent form. Accordingly, it is respectfully requested that the objection to claim 16 be reconsidered and withdrawn.

Rejection of Claims 13-18, 20, 23, and 27 Under 35 USC §112, first paragraph

Claims 13-18, 20, 23, and 27 have been rejected under 35 USC §112, first paragraph "because the specification, while being enabling for methods of using some enhancing agents to ameliorate or treat some autoimmune diseases, does not reasonably provide enablement for methods of using any bacterial enhancing agents to prevent any autoimmune disease." It is the Examiner's position that "the applicant has not shown that one skilled in that art may treat or prevent any autoimmune disease by administering to the subject any bacterial cell or substance

derived therefrom. Nor has the applicant provided adequate guidance as to what bacterial or parasitic species or strains, or substances, will be effective in the claimed methods." The Examiner further states that "the applicant has provided no disclosure that would support the claim that any autoimmune disease may be treated or prevented with any bacterial strain, or even any of those 6 strains that are named in the claims." This rejection is respectfully traversed.

The pending claims pertain to methods of preventing the development of an immune response to a self antigen in a subject comprising, administering an enhancing agent which activates NK-T or CD25+ cells, wherein the enhancing agent is a bacterial cell lysate or is derived from a multicellular parasite. The claims also pertain to methods of ameliorating the symptoms of an ongoing immune response to a self antigen in a subject comprising administering an enhancing agent to the subject which activates NK-T or CD25+ cells, wherein the enhancing agent is a bacterial cell lysate or is derived from a multicellular parasite.

In order for a claimed invention to be enabled, the standard is not whether or not experimentation is necessary to practice the claimed invention. Rather, the standard is whether or not the experimentation necessary to practice the claimed invention is undue (See *In re Wands*, 858 F.2d at 737). Thus, enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. *In re Wands*, supra. Applicants provide sufficient guidance such that one of ordinary skill in the art could practice the claimed methods without undue experimentation. Applicants teach exemplary molecules which increase the activity of NK-T cells and CD25+ cells. For Example, such agents are described at pages 14-18 of the specification.

Applicants also teach various ways in which one of ordinary skill in the art could identify other compositions which could activate NK-T cells and CD25+ cells, for example by determining the ability of the candidate agent to stimulate NK-T cell clones (e.g., using well known techniques such as those pages 18 and 19 of the specification). One of ordinary skill in the art, armed with the knowledge of one of the ordinarily skilled artisan and given the teachings and methods disclosed in Applicants specification, would be able to practice the claimed methods using no more than routine experimentation.

Moreover, under 35 U.S.C. §112, first paragraph, the Examiner has the "initial burden of setting forth a reasonable explanation as to why the scope of protection provided by [the claims] is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). Specifically, in *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995), it was held that:

> *Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.*

Additionally, the court stated that in the absence of a reason to doubt the objective truth of the teachings contained in the specification, the methods of making and using the claimed invention must be taken as complying with the requirements of §112, first paragraph. The Examiner has not met this burden, accordingly, the claims must be taken as complying with §112, first paragraph.

In view of the foregoing, it is respectfully requested that the above rejection be reconsidered and withdrawn.

Rejection of Claims 13-18, 20, and 23 Under 35 USC §102(b)

Claims 13-18, 20, and 23 have been rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent Number 5,830,475, issued to Aldovini et al. (Aldovini) and by published PCT application WO 85/05034, naming Stanford et al. as inventors. This rejection is respectfully traversed.

The Examiner states that:

> Aldovini teaches that whole recombinant mycobacterial cells may used as live recombinant vaccine vesicles (col. 1, lines 33-40), while Stanford teaches that the bacteria, and solutions of the fractionated bacteria (therefore lysates) may be used in treatments and vaccines (p. 2, lines 18-22). As the references teach that the bacterial solutions may be used both as a vaccine, and for curative purposes, they inherently teach that the solutions may be administered to both subjects known to be at risk for an autoimmune disorder (curative), and those not known to be at risk (vaccine). Stanford further teaches that the compositions of the mycobacteria may be administered orally.

The pending claims all require that the enhancing agent be in the form of a ***bacterial cell lysate*** or be derived from a multicellular parasite. (Applicants understand that the claims are currently being examined to the extent that they read on use of a bacterial cell lysate. Accordingly, the arguments below will reflect this).

Stanford et al. teach the use of Mycobacterial cells or fractionated cells; contrary to the suggestion made by the Examiner, the Stanford reference is devoid of any teaching or suggestion that bacterial cell lysates could be used. The reference teaches that such cells could be "used as such or fractionated by the use of certain solvents to give a precipitate and a ***water soluble fraction***, which latter is suitable for various vaccinations and curative purposes." See page 2, lines 18-22, emphasis added. Accordingly, the reference teaches only the use of whole cells or water soluble fractions thereof and not cell lysates. Aldovini et al. teaches the use of

recombinant Mycobacteria. Therefore, the cited references fail to teach or suggest bacterial cell lysates.

Moreover, the Stanford reference teaches that *Mycobacterium tuberculosis* can induce arthritis and that certain cells can protect against the development of mycobacterium-induced arthritis; the reference fails to teach or suggest preventing the development of an immune response to a self antigen by administering an enhancing agent which activates NK-T or CD25+ cells. Similarly, the Aldovini reference teaches the use of modified mycobacteria which produce stress proteins to induce tolerance (column 11) and fails to teach or suggest preventing the development of an immune response to a self antigen by administering an enhancing agent which activates NK-T or CD25+ cells.

With respect to the Van Eden et al. reference not relied upon by the Examiner but "considered redundant to the Stanford document above." The Applicants would like to make the following remarks of record. The Van Eden et al. reference also fails to teach or suggest the use of a bacterial cell lysate. The reference teaches purified BCG antigen A polypeptides and their methods of use. Accordingly, this reference is also devoid of any teaching with respect to bacterial cell lysates. In addition, the reference teaches that antigen A can prevent induction of mycobacterium-induced arthritis and does not pertain to preventing the development of an immune response to a self antigen by administering an enhancing agent which activates NK-T or CD25+ cells.

Accordingly, it is respectfully requested that the rejection of claims 13-18, 20, and 23 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent Number 5,830,475, issued to Aldovini et al. (Aldovini) and by published PCT application WO 85/05034, naming Stanford et al. as inventors be reconsidered and withdrawn.

Rejection of Claims 13, 14, 16, 20, 21, and 27 Under 35 USC §102(e)

Claims 13, 14, 16, 20, 21, and 27 have been rejected under 35 USC §102(e) over Watson et al. This rejection is respectfully traversed.

The Examiner states that Watson:

> teaches that derivatives of Mycobacteria vaccae cells may be administered to a subject to prevent and treat these diseases. Abstract; col. 4, lines 45-51 (allergic rhinitis includes hay fever); and col. 6, lines 44-49. Among the derivatives that may be used are mycobacterial cells subjected to alkaline or acidic hydrolysis. Thus, the patent teaches the use of agents derived from mycobacterium to treat asthma, hay fever, and allergic rhinitis. The patent further teaches that the composition may be administered through the nose or mouth, thus orally. Col. 7, lines 27-30.

As set forth above, the pending claims all require that the enhancing agent be in the form of a ***bacterial cell lysate.*** Watson et al. teach the use of compositions comprising derivatives of ***delipidated and deglycolipidated*** *M. vaccae* cells. The reference fails to teach or suggest the use of a bacterial cell lysate. Moreover, the teachings of the reference pertain to asthma, and allergic rhinitis, not immune responses to a self antigen. Accordingly, it is respectfully requested that the rejection of claims 13, 14, 16, 20, 21, and 27 under 35 USC §102(e) over Watson et al. be reconsidered and withdrawn.

Rejection of Claims 13, 14, 16, 17, 20, and 23 Under 35 USC §102(b)

Claims 13, 14, 16, 17, 20, and 23 have been rejected under 35 USC §102(b) over Qin. This rejection is respectfully traversed.

The Examiner states that the reference "discloses that the administration of Complete Freunds Adjuvant helps to prevent and to delay onset of (ameliorate) an autoimmune disease - insulin-dependent diabetes mellitus." The Examiner continues "[a]s the adjuvant contains a mycobacterial cell wall, and as the application contains no definition for a bacterial lysate that is contradictory to the inclusion of the adjuvant in the definition, the reference contains a bacterial lysate."

As set forth above, the pending claims all require that the enhancing agent be in the form of a ***bacterial cell lysate.*** In contrast to the Examiner's suggestion, the Qin reference fails to teach or suggest the use of a cell lysate. The term "cell lysate" is known to those of skill in the art to mean the material that results when cells are subjected to lysis. The reference teaches the use of complete Freund's adjuvant, which comprises mycobacterial cell wall. The reference fails to teach or suggest the use of a bacterial cell lysate, which would comprise all the other components of lysed bacterial cells. Accordingly, it is respectfully requested that the rejection of claims 13, 14, 16, 17, 20, and 23 under 35 USC §102(b) over Qin et al. be reconsidered and withdrawn.

Rejection of Claims 13-18, 20, and 27 Under 35 USC §102(e)

Claims 13-18, 20, and 27 have been rejected under 35 USC §102(e). This rejection is respectfully traversed.

The Examiner states that "Delcayre describes the use of polypeptides and polynucleotides derived from Mycobacteria to treat diseases, including asthma and allergic rhinitis." The Examiner further states that "[t]he patent teaches that the vaccines compositions may be formulated for oral administration" and continues "because the patent teaches the use of, and methods using, proteins derived from Mycobacteria to treat asthma and allergic rhinitis, and the claims rejected read on substances derived from Mycobacteria, the claims are anticipated by the reference."

As set forth above, the pending claims all require that the enhancing agent be in the form of a ***bacterial cell lysate.*** Delcayre et al. teach the use of compositions comprising Polypeptides and polynucleotides isolated from *Mycobacterium vaccae*. The reference fails to

teach or suggest the use of a cell lysate. In addition, the reference pertains to enhancement of immune response to heterologous antigens (column 10), not to preventing the development of an immune response to a self antigen by administering an enhancing agent which activates NK-T or CD25+ cells. Accordingly, it is respectfully requested that the rejection of claims 13-18, 20, and 27 under 35 USC §102(e) over Delcayre et al. be reconsidered and withdrawn.

Rejection of Claims 13-18, 20, 23, and 27 Under 35 USC §103(a)

Claims 13-18, 20, 23, and 27 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Number 6,433,013 issued to Verschoor et al. (Verschoor), in view of Aldovini; and further in view of Watson and Qin. This rejection is respectfully traversed.

The Examiner relies on the secondary references as set forth above. The Examiner relies of Verschoor as teaching "that certain cell membrane molecules from mycobacterial cell membranes may be used to treat autoimmune disorders, including allergies. Further, the reference teaches that the cell membrane lipids may be administered with a bacterial protein derived from a Mycobacterium." The Examiner continues, "[b]ecause Aldovini teaches that Mycobacterium are highly effective adjuvants [ ], and because Verschoor suggests the use of the bacterium as adjuvants it would have been obvious to one of ordinary skill in the art to use these compositions together to treat autoimmune allergies." The Examiner acknowledges that the teachings do not teach the use of bacterial lysates. The Examiner further states that:

> Watson taught that derivatives of mycobacterium could be used to treat hay fever, asthma, and allergic rhinitis. Qin taught that administration of Complete Freunds Adjuvant (which contains mycobacterial cell wall fragments) helps to prevent and to delay onset of (ameliorate) an autoimmune [sic]. Abstract. Watson

> teaches that mycobacterial cell adjuvants comprising cell wall fragments (bacterial lysates) of these bacteria are likewise effective adjuvants. It would therefore have been obvious to one of ordinary skill in the art to use the cell components as the adjuvant in the method of Verschoor. One of ordinary skill in the art would have had a reasonable expectation of success in the combination as all of the elements combined were known to be effective in the treatment, and no reason existed to indicate that combing the elements would yield less effective results.

To establish a *prima facie* case of obviousness for the claimed invention, there must have been some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in the manner proposed by the Examiner. Second, there must have been a reasonable expectation of success at the time the invention was made. ***Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.*** See M.P.E.P. 2143. The prior art must suggest "to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process" and "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.* 837 F.2d 469. 473, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

The pending claims are directed to methods of preventing the development of an immune response to a self antigen in a subject comprising, administering an enhancing agent which activates NK-T or CD25+ cells, wherein the enhancing agent is a bacterial cell lysate or is derived from a multicellular parasite. The claims also pertain to methods of ameliorating the symptoms of an ongoing immune response to a self antigen in a subject comprising administering an enhancing agent to the subject which activates NK-T or CD25+ cells, wherein the enhancing agent is a bacterial cell lysate or is derived from a multicellular parasite.

As set forth above, none of the secondary references teach or suggest the use of bacterial cell lysates. The teachings of the Verschoor et al. reference fail to make up for this deficiency. The Verschoor reference teaches the use of compositions comprising ***purified lipid***

cell-wall components or analogs or derivatives thereof and fails to teach or suggest the use of a bacterial cell lysate. Accordingly, the cited art fails to teach all the limitations of the claims as required by M.P.E.P. 2143. Therefore, the claims are not obvious in view of the art of record.

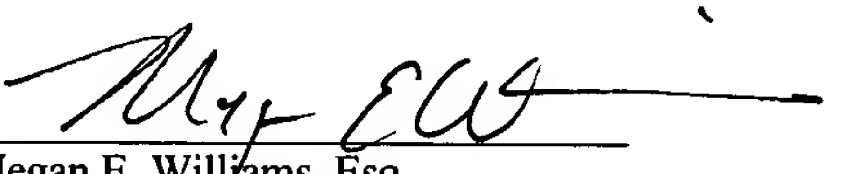
Moreover, Applicants point out that, at the time the invention was made there was no motivation or reasonable expectation of success in making the claimed invention. Watson et al. (cited by the Examiner) teaches that differences were observed between using whole heat-killed *M. vaccae* and delipidated *M. vaccae* in terms of the cytokine secretion profiles obtained. In addition, Verschoor et al. (cited by the Examiner) also teaches that different components of *M. tuberculosis* result in very different immune responses. Given the different outcomes observed when different forms of antigen were administered, one of ordinary skill in the art would not have been motivated to modify the teachings of the art to arrive at the use of the bacterial cell lysates presently claimed. Accordingly, one of ordinary skill in the art would not have been motivated to use lysate of whole cells, nor would there have been any reasonable expectation of success that such a method would have been successful in increasing the activation of NK-T or CD25+ cells as claimed.

Moreover, Applicants point out that the Verschoor et al. Aldovini; and Watson et al. references do not pertain to preventing the development of an immune response to a self antigen in a subject comprising, administering an enhancing agent which activates NK-T or CD25+ cells to the subject. Accordingly, at the time the invention was made, there was no motivation present in the art to modify the teachings present in these references to arrive at the claimed invention.

SUMMARY

If a telephone conversation with applicant's agent would expedite the prosecution of the above-identified application, the examiner is urged to call applicant's agent at (617) 227-7400.

Respectfully submitted,



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Dated: **March 10, 2003**

APPENDIX A
VERSION SHOWING CHANGES MADE

13. (Amended) A method of preventing the development of an [autoimmune disorder] immune response to a self antigen in a subject comprising, administering an enhancing agent which activates NK-T or CD25+ cells to the subject, [wherein the enhancing agent comprises a bacterium or a multicellular parasite or a substance derived therefrom] wherein the enhancing agent is a bacterial cell lysate or is derived from a multicellular parasite.

14. (Amended) The method of claim [13] 17, wherein the subject is known to be at risk for the development of an [autoimmune disorder] immune response to a self antigen.

15. (Amended) The method of claim [13] 17, wherein the subject is not known to be at risk for the development of an [autoimmune disorder] immune response to a self antigen.

16. (Amended) A method of ameliorating the symptoms of an ongoing [autoimmune disorder] immune response to a self antigen in a subject comprising administering [the enhancing agent of claim 13 to the subject] an enhancing agent which activates NK-T or CD25+ cells to the subject, wherein the enhancing agent is a bacterial cell lysate or is derived from a multicellular parasite.

17. (Amended) The method of claim 13 or 16, wherein the enhancing agent is a [substance derived from a bacterium] bacterial cell lysate.

18. (Amended) The method of claim [13 or]17, wherein the enhancing agent is administered orally.

20. (Amended) The method of claim [13 or] 17, wherein the [enhancing agent] bacterial cell lysate is derived from a bacterium belonging to the genus *Mycobacteria*.